Overcoming the transmembrane protein degradation challenge: A novel ERAD-based approach

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Targeted protein degradation (TPD) has emerged as a paradigm-shifting approach for selective degrading proteins of interest (POIs) over the past two decades.[1] While proteolysis-targeting chimeras (PROTACs) and molecular glues have demonstrated remarkable success against intracellular targets,[2] efficiently degrading transmembrane proteins, which constitute approximately 40% of the druggable genome and are implicated in a variety of diseases,[3] remains a persistent challenge.

In a recent study published by Song et al. in Cell,[4] the authors introduce a conceptually distinct TPD strategy that directly addresses this limitation. By engineering chimeric molecules that hijack the endoplasmic reticulum-associated degradation (ERAD) pathway, the authors establish a platform termed ERAD-engaging chimeras (ERADECs) and demonstrate its utility through potent degradation of the immune checkpoint protein PD-L1.[4] This work not only expands the TPD toolbox but also redefines the conceptual framework

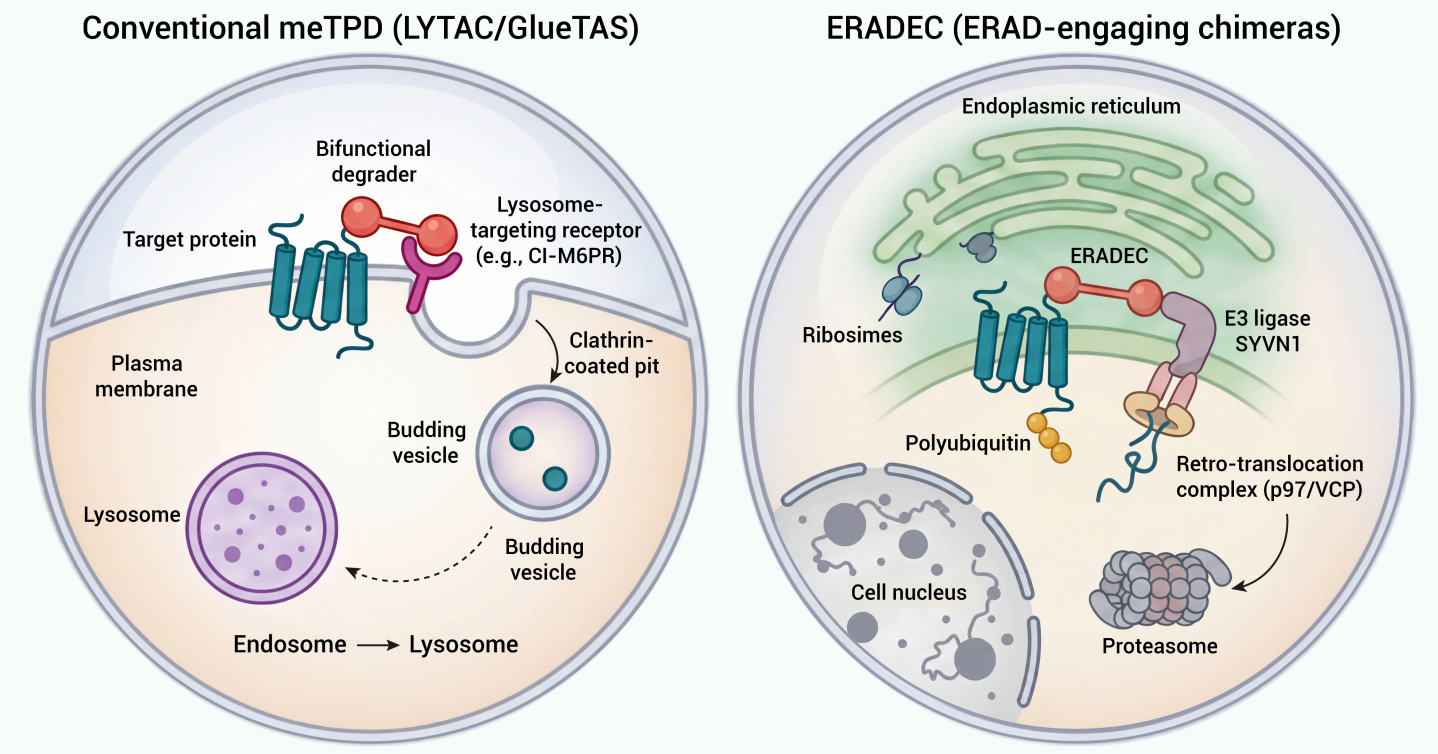

Figure 1. Mode of action of ERADEC and conventional meTPD platforms ERADEC, ER-associated degradation engaging chimeras; meTPD, targeted protein degradation in the transmembrane and extracellular space. The meTPD includes lysosome-targeting chimera (LYTAC), covalently engineered nanobody chimera (GlueTAC) etc.

for degrading transmembrane proteins.

Existing TPD strategies targeting transmembrane proteins, such as lysosome-targeting chimeras (LYTACs), or covalently engineered nanobody chimeras (GlueTACs), typically engage targets at the plasma membrane and direct them to the lysosome via endocytosis. However, these approaches act downstream of protein synthesis and are constrained by endosomal recycling as well as continuous replenishment from nascent protein pools.

ERADECs adopt a fundamentally different strategy. By acting at the endoplasmic reticulum (ER), where most transmembrane proteins are synthesized and folded, these degraders intercept the targets before they reach the cell surface. The ER is equipped with a sophisticated quality control system, termed ERAD, that degrades misfolded or unassembled proteins.[5] ERADECs hijack this pathway by tethering a target transmembrane protein to the ER-resident E3 ubiquitin ligase SYVN1, thereby marking a properly folded protein as aberrant and targeting it for proteasomal degradation.

Unlike previous platforms that target the plasma membrane (LYTACs, GlueTACs) or the cytosol (PROTACs), ERADECs act at the endoplasmic reticulum, where is the site of membrane protein synthesis. By hijacking the ERAD quality control pathway, they induce degradation of properly folded transmembrane proteins before they reach the cell surface (Figure 1). This subcellular strategy distinguishes ERADECs from platform extensions that merely optimize existing modalities. While the long-term impact of ERADECs will depend on their generalizability and safety, their mechanistic novelty warrants recognition as a potentially transformative direction in TPD.

The mechanistic characterization of the ERADEC platform in this study is thorough and informative. The authors initially identified desonide, a glucocorticoid, as a degrader of mutant huntingtin (mHTT) by interacting with the ERAD E3 ligase SYVN1. This accidental discovery provided a starting chemical warhead for hijacking the ERAD pathway. Through systematic structure-activity relationship studies, they converted this micromolar-affinity binder into highly potent PD-L1 degraders, such as compounds P2, which achieved sub-nanomolar the half-maximal degradation concentration (DC_{50}, 0.2 nM) values and greater than 90% degradation efficacy (D_{max}, 90.5%).

A critical factor underlying this substantial increase in potency is ternary

complex cooperativity. Biophysical experiments revealed that although the binary affinity of P2 for SYVN1 or PD-L1 was moderate, the affinity of the ternary complex formed by PD-L1, P2, and SYVN1 was markedly enhanced, with a calculated cooperativity factor (α) of 38.3. This cooperative binding, in which complex formation is thermodynamically favored over the sum of its binary interactions, is a characteristic feature of highly effective PROTACs, which typically exhibit α values ranging from ~10 to > 100. The ERADEC platform thus demonstrates that even a binder with modest binary affinity can serve as the basis for a highly potent degrader. However, it should be noted that in vitro affinity measurements may not fully recapitulate the cellular environment, where factors such as local concentration, membrane context, and ERAD machinery components can modulate ternary complex stability.

In addition, the authors identified the binding site of ERADECs within the transmembrane domain of SYVN1, specifically involving residue Y227. This finding extends the study beyond cellular observations and provides a molecular basis for understanding ERADEC function. Such detailed structural insight is valuable for future rational design efforts, including the optimization of linkers and warhead binding properties.

The therapeutic potential of ERADECs is well supported by in vivo data. In a xenograft mouse model, the PD-L1 degraders suppressed tumor growth and exhibited greater efficacy than the clinically approved PD-L1 antibody atezolizumab. This enhanced antitumor activity, combined with the favorable drug-like properties of small molecules, including synthetic accessibility and potential for oral bioavailability as well as lack of immunogenicity, supports ERADECs as a promising therapeutic modality.

The authors also addressed potential specificity concerns. Because the warhead desonide is a known glucocorticoid receptor agonist, they performed a series of control experiments to confirm that the degradation activity was independent of glucocorticoid receptor engagement. These included glucocorticoid receptor knockdown, pharmacological antagonism, and the use of a structural analog prednisolone that binds the receptor but not SYVN1, which failed to induce degradation. Such rigorous controls highlight the importance of mechanistic validation when repurposing known ligands for new applications.

Finally, the modularity of the ERADEC platform is demonstrated by the successful development of a degrader targeting EGFR using a distinct ligand (canertinib). This result suggests that the ERADEC concept is adaptable and may be extended to a broad range of transmembrane proteins for which small-molecule binders are available or can be developed. Accordingly, this approach may enable the targeting of transmembrane proteins considered undruggable or resistant to conventional degradation strategies.

The introduction of ERADECs also raises several questions that will shape the future of this technology. First, ERAD is not monolithic but comprises three sub-pathways (ERAD-L/M/C). SYVN1 primarily operates in ERAD-M and ERAD-L, justifying its use for a transmembrane target like PD-L1. However, the ER contains at least 20 distinct E3 ligases with different substrate preferences and tissue expression profiles. For example, AMFR is enriched in certain cancers, whereas SYVN1 is ubiquitous. This raises the possibility of designing ERADECs that engage alternative E3 ligases for tissue-restricted degradation, improving therapeutic windows. Systematic profiling of E3 ligase expression will be critical to guide such efforts. Second, the claimed kinetic advantage of intercepting newly synthesized proteins before they reach the plasma membrane remains largely conceptual. Song et al. showed that PD-L1 reduction takes >12 h,[4] comparable to its total half-life (~17-18 h). Without pulse-chase experiments tracking the ER-retained pool separately, it is unclear whether ERADECs accelerate nascent chain degradation or merely prevent replenishment while surface PD-L1 turns over normally. Until such data are available, this advantage should be framed as plausible rather than proven. Third, chronic ERAD engagement raises multiple concerns: potential exhaustion of ERAD capacity could impair clearance of misfolded proteins; subtle UPR activation may occur even without overt ER stress markers; delivery to the ER compartment demands distinct physicochemical properties (e.g., membrane permeability) not typically optimized for cytosolic drugs; and prolonged use may select for resistance via SYVN1 upregulation or target mutations. While the study showed no obvious toxicity, these challenges warrant systematic investigation before clinical translation.

Nonetheless, the work by Song et al.[4] represents a notable advance in the field. By demonstrating how mechanistic understanding of a cellular quality control pathway can be leveraged to develop a targeted degradation strategy, this work provides a clear example of translation from fundamental biology to therapeutic innovation. The ERADEC platform addresses a key limitation in current TPD approaches by redirecting an endogenous ER quality control mechanism toward selective degradation of transmembrane proteins. More broadly, this study illustrates how revisiting established cellular pathways can yield new strategies for therapeutic intervention.

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G.Q. wrote the manuscript and drawn the picture of the commentary.

DECLARATION OF INTERESTS

The author declares no competing interests.